- Pts under 18yo do NOT need parental consent if they are emancipated (married, etc), have an STD and need Dx/Tx, want contraception, are pregnant, have an acute pysch illness or they themselves are a parent
- Determine if pt has "Decision Making Capacity" and if not then find living will / advanced directives (specifies patient's wishes) and if not available then durable power of attorney (any chosen person (proxy/surrogate), i.e. specific family member, friend, etc, ends when pt dies, person should carry out wishes of pt and if you don't know then act in best interest, supersedes surrogate family member) or if not available then next surrogate family member (**spouse → adult child → parent → siblings**) if not life threatening but if life threatening and no one is there then act w/ non-maleficence (above all do no harm, eg. giving narcotic to a drug addict) which overrides Futility (therapy is no good therefore even if the pt wants it you should not provide it regardless of their autonomy, eg. giving HCV Tx to a pt w/ metaststic HCC) which overrides Respect for Autonomy (act so that the consequences of a physician's behavior toward the pt is expected to produce more good than harm as understood from the **pt's** perspective, generally respect for autonomy outweighs beneficence however futility outweighs respect for autonomy, eg. Jehova's witness refusing transfusing) which overrides beneficence (act so that the consequences of a physician's behavior towards the patient is expected to produce more good than harm as understood from the **physician's** perspective, however the ethical concept of beneficence must be balanced against the concept of respect for autonomy, eg. banding a variceal bleeder when a pt cannot give consent)
- Confidentiality can be broken if pt wants to harm himself or another then call police or has a dz that is at risk to another (e.g. HIV, TB, STD) then notify that person thru public health
- Intimate MD-Pt relationships, terminate professional relationship, wait a period of time, then pursue relationship if you want, you can't do both at the same time, hence not impossible (This is the current recommendation!!!)
- Always disclose medical errors and say "I am sorry"
- Clinical Research: **Nuremberg Trial** (23 Nazi doctors convicted for crimes against humanity based on research done on concentration camp prisoners, NB other unethical experiments: Tuskegee Syphilis Study, cancer transplantation, Vinberg Procedure, infection exposure) this led to the **Nuremberg Code** in 1935 (voluntary consent, no coercion, beneficence and nonmaleficence, do not include incompetent persons including children, prisoners, retarded, results should be anticipated to fruitful results for society, avoid suffering and injury, experiment should be based on existing knowledge, risk should not exceed benefit, voluntary withdrawal should be allowed) and **Declaration of Helsinki** in 1975 (similar to the Nuremberg Code) which is used by the **Institutional Review Board (IRB)** (peer review of research on humans, should include abstract/background, population studied, subject selection process, potential benefits, anticipated risks, safety precautions, data monitoring, stopping rules, advertisements, rights of withdrawal, injury compensation, assurance of confidentiality, research consent form (written at a 7th grade level, name, investigators, sponsor, contact #, background, risks/benefits, costs, alternatives))
- Procedure Informed Consent (remember that what we do is considered assault and battery, "competent pt with power of refusal demonstrates understanding of R/B/L/A/P/P and voluntarily w/o coercion/manipulation agrees to undergo the procedure", risk should include probability and severity, Malpractice/Tort Law (battery or negligence), lack of decision making capacity (decision should be based on what pt wanted) or implied consent during an emergency, sometimes a psych referral is needed)
- When u terminate a pt you must formally notify the pt, help them find a new doctor, take care of pt until they find a new doctor and transfer records to new doctor
- You can't refer a patient to a physician owned center unless you work there

EBM

- Use of mathematical research derived from populations to inform decisions on individuals

Literature Search

- **Clinical action should be based on EBM and or if not present then Formal Consensus from Committees**
- **Journal Databases**
  - Ovid Medline (Advanced) Pubmed Medline (Basic)
  - Scopus
  - Scirus
- **Other**
  - Micromedex (search of pharm)
  - www.clinicaltrials.gov (lists current medical trials)
  - National Standard (search of alternative medicine)
- **Approach**
  - Boolean Operators: AND, OR, NOT, ( ), " "
  - Find the MeSH keywords that correspond to the topic you want to search as all articles are arranged into a tree based on those MeSH keywords
  - Use limiters like language, dates, etc

Statistics

- Types of Studies
  - **Prognosis: survival curves (usually ? studies)**
  - **Harm: odd's ratios (usually case control studies) and RRR/ARR (usually cohort studies) or just cross-sectional surveys or case report/series (unethical to do prospective studies)**
  - **Diagnostic Test: Sens/Spec/Likelihood Ratios (usually ? studies)**
  - **Therapy: RRR/ARR/NNT (usually DBRPCT)**

- What is the study?
  - Secondary (summarize and draw conclusions from primary studies, ranked in order of value)
    - **Overviews aka Systematic Reviews and Meta-Analyses**
      - The Cochrane Library (read the "plain language summary" following the abstract and "forest plot" which graphically displays the results of primary studies)
      - Up-To-Date
      - DynaMed
      - DARE
      - Clinical Evidence
      - ACP PIER
      - National Guideline Clearinghouse
    - **Guidelines**
    - **Expert Opinion**
  - Primary (first hand research, ranked in order of value, **Hypothesis** (Effectiveness of New Tx/Dx against Dz or RF/Etiology of Dz)
    - Controlled Studies (GRADE A evidence)
      - **Double Blinded Randomized Controlled Trials** (DBRCT): in which an intervention is offered to a group of people who are then followed up to see what happens
        - Potential Problems: too short, surrogate end points may not reflect the most appropriate outcomes, pts were not truly randomized, failure to blind, exclusionary/inclusionary criteria may lead to results that do not apply to your own practice, etc
        - RCT are usually the gold standard but not all studies need to be RCT and sometimes it's inappropriate (studies below)
        - RCTs should follow a very specific format (defined by the CONSORT statement) and include: title, abstract, methods, objectives, participants, setting, intervention, outcomes, sample size, masking, statistical methods, details of randomization, implementation, results, flow diagram, protocol deviations, recruitment dates, baseline data, numbers analyzed, outcomes, ancillary analysis, adverse events, interpretation
        - Intention To Treat Analysis (all pts are included in final data analysis regardless of whether they completed the trial) vs Per Protocol Analysis (only pts who complete the trial according to protocol are analyzed) NB often PPA shows statistically significant result but the ITTA does not and you want the ITTA to show statistically significant result
        - Crossover (each participant received both the intervention and control treatment often separated by a washout period on no treatment)
        - Placebo Controlled or Sham Operation
        - Paralleled Comparison (each group receives a different Tx) vs Paired/Matched Comparison (one group receives a Tx and the other doesn't?) vs With-In Comparison (every participant is assessed before and after the intervention)
    - Observational Studies (difficult to identify two groups with everything the same except for the one single difference being studied, most of the controlling is done during the analysis stage where complex statistical adjustment is made for baseline differences in key variables) (GRADE B/C evidence)
      - **Cohort Studies**: group of people are selected on the basis of differences in their exposure to something and followed prospectively over time to see how many in the group develop a dz
        - Relative Risk: risk of dz in exposed group compared w/ risk of dz in unexposed group
        - Biases: confounding variables and surveillance bias
        - good for determining the etiology of a common dz
      - **Case Control**: pts w/ or w/o a disease are identified and matched w/ controls, retrospective data is then collected on past exposure to determine a possible etiology or risk factor for the dz
        - Odd's Ratio: odds of a pt w/ a dz having a RF compared to the odds of apt w/o the dz having the same RF
        - Biases: recall bias, interviewer bias, unmeasured confounding variables
        - good for determining the etiology of a rare dz
      - **Cross-Sectional Surveys**: a representative sample of a population is interviewed
      - **Case Reports/Series:** a description of patient or group of patients with a rare disease, good b/c can be done quickly but overall weak
    - Other
      - **Bench/Lab Experiments** on Animals/Volunteers
  - **Was it original?** If there are similar studies how is this one different (longer, bigger, more rigorous methods, different population, etc)?
  - Who is the study about b/c research on one population may not translate to your practice? How are the studied pts different (more/less ill, ethnicity, etc)? Where the participants recruited resulting in a certain bias? Who was included/excluded in the study?
- What is the hypothesis?
  - **Alternative** (study is trying to prove correlation)

- **Null** (study is trying to prove NO correlation aka that the new Tx/Dx is not effective against Dz or the RF/Etiology is not accurate of Dz)

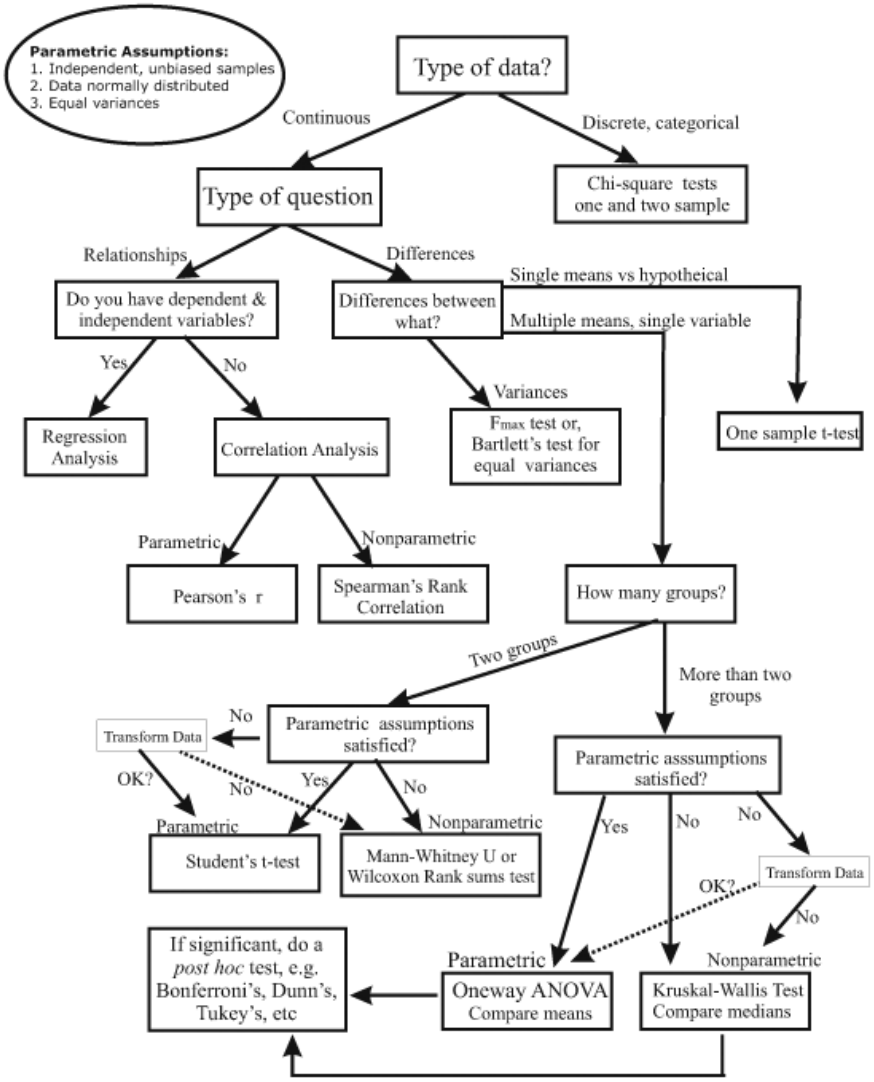
- How was the hypothesis checked?
  - **Experimental Study** for Tx/Dx against Dz
    - **Double-Blind-Randomized Well-Matched-Placebo Control Trial**
  - **Observational Study** for RF/Etiology of Dz
    - **Prospective Study w/ Cohorts** (difficult, slow study)
    - **Retrospective Study w/ Case Control** (easy, fast study)
- Was it well designed? What was the intervention being compared to? What primary/secondary outcomes were measured? Were there surrogate end points? Where the end measurements objective or subjective? Where the pts and doctors blinded?
  - There should be a table comparing baseline characteristics (eg. gender, age, etc and every key prognostic variable) in the two groups and there should be no statistical difference in these characteristics
  - Data can be parametric (nl distribution) vs non-parametric (non-nl distribution, eg. rank order)
- How was the data analyzed?
  - Before you do a study you need to do a sample size calculation (done by statisticians) based on four parameters (treatment effect (d), standard deviation (s), alpha level (usually 0.05), beta level (usually 0.2)) b/c alpha and beta levels are usually fixed the formula becomes… n (number) = $16 \times s^2/d^2$
  - What is the data type aka variable?
    - Quantitative Variables evaluated by Parameteric Statistics [Continuous Variable (can be measured to as many decimal places as the measuring instrument allows, eg. degrees, NB these can be interval variables, eg heart beats or ratio variables, eg. hearts beats per minute) vs Categorical Variable (you can only have whole numbers, eg. number of children, you can't have 2.1 children)], variables follow a Gaussian (Bell Curve) Distribution = perform two general types of statistics (NB curves can be non-Gaussian w/ skews or bimodal)

Continuous	t-Test (compares means) or Mann-Whitney U Test or Wilcoxin Rank Sum Test (compares medians)
Categorical	Chi-Square Test or Fischer Exact Test (compares the frequency of variables)

	Dichotomous	Gaussian Continuous
Dichotomous	**Chi Square Test**	**Student's T Test eg. Mann-Whitney U Test**
Multi-Normal		**ANOVA F-Test**
Multi-Ordinal		**ANOVA F-Test**
Gaussian Continuous		**Regression Analysis**

	Outcome Measure	Hypothesis Test	Measure of Effect Size
Categorical: Nominal	1. Proportion 2. Rate	1. Chi Square Test 2. Fischer Exact Test	1. Ratio or difference in proportions 2. Odds Ratio
Categorical: Ordinal	1. Proportion 2. Rate 3. Median 4. Percentiles	1. Wilcoxin Rank Sum Test or Mann Whitney U Test 2. Chi Square Test	1. Ratio or difference in proportion 2. Odds Ratio 3. Difference in Medians or Percentile
Continuous: Non-Normal Distribution	1. Proportion 2. Rate 3. Median 4. Percentiles	1. Chi Square Test	1. Ratio or Difference in proportion 2. Odds Ratio 3. Difference in medians or Percentiles 4. Regression Coefficients (linear regression and correlation)
Continuous: Normal Distribution	1. Proportion 2. Rate 3. Median 4. Percentiles 5. Mean	1. Student T Test	1. Ratio or difference in proportion 2. Odds Ratio 3. Difference in medians or percentiles 4. Regression Coefficients (linear regression and correlation)

Flow Chart for Selecting Commonly Used Statistical Tests



- Descriptive Statistics: terms used to just communicate the results in a meaningful way w/o attempting to generalize beyond the sample of individuals studied to any other group of people
  - **Mean** (avg), **Mode** (most common value), **Median** (middle value) NB m=m=m if no skew but if +/- skew then m≠m≠m
  - Deviation (tells on average how much each datum differs from the mean)
    - Range = distance from highest and lowest variable
    - Average Deviation (AD) = sum of the differences b/t each datum and the mean divided by the number of values aka average of the differences = always 0 b/c negative and positive cancel each other out hence use SD → **Standard Deviation (SD/s/σ)** = similar to AD but takes into account potential negative values by squaring the differences to remove the negative sign and then converting back by taking square root of the end value (1/2/3SD holds 90/95/97% of values)

$$s=\sqrt{\frac{\sum(X-M)^2}{n}}$$

- You can create a curve if you know the mean and SD and there is a Gaussian distribution to the data and it turns out that for every curve 68% of values fall w/in 1SD and 95.5% of values fall w/in 2SD w/ 2.3% of values at each tail
- **Standard Score (z)** = difference b/t a datum and the mean divided by the SD = gives you a score that can be used to compare the results of tests that use different scales

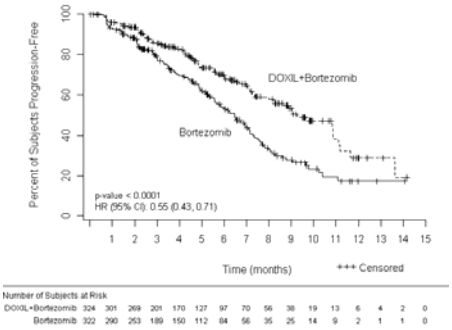
$$z = \frac{X - \mu}{\sigma}$$

- Inferential Statistics (two main goals below)
  - (1) to determine if the difference b/t the groups is due to the experimental intervention or just by chance b/c there is always some experimental error associated with the process of measurement
    - **Standard Error (SE) of the Mean** = when you take a sample and calculate the mean it is only the mean of that sample and not of the entire population b/c of "random error effects" but as you calculate the means for many samples the means themselves create a bell shaped curve clustering around the true mean, the SE is the SD for this curve (NB Central Limit Theory states that if the samples sizes are large the means will be normally distributed regardless of the shape of each sample)

$$SE_m = \frac{s}{\sqrt{n}}$$

    - Z-test?
    - p = chance or probability that the difference between the groups was by chance and that they really weren't different → if <0.05 then the chance is <1/20 which is really unlikely therefore there likely was a true difference → reject the "null hypothesis" (H_0)and support the "alternative hypothesis" (H_1)
      - alpha level = the probability of incorrectly rejecting/accepting the null/alternative hypothesis creating a Type I error (agreed upon limit is <0.05)
        - NB "certainty" = 1-alpha = probability you will not make a Type I error
      - beta level = the probability of incorrectly accepting/rejecting the null/alternative (agreed upon limit is 0.1)
        - NB "power" = 1-beta = probability you will not make a Type II error
    - **95% CI (Confidence Interval) = Sample Mean ± 1.96 x SE** (the range in a study's observed value such that 95% of the time a measured value when restudied will fall into this range aka w/in 2SD) eg. ABI of 4.5 (95%CI, 3.8-5.2) the more narrow the better, determined by complex formulas, usually the larger the sample size the narrower the CI (NB CI can be determined for any statistical test (eg. ARR, NNT, sensitivity, specificity, etc) and tells you whether the evidence is strong or weak)
      - **If CI for RBI does not cross 1 then it is statistically significant**
      - **If CI for ABI does not cross 0 then it is statistically significant**
  - (2) to see if the results can be generalized to other individuals but one must be confident that the pts studied are representative of the class the investigator wants to describe and that the pts studied underwent a random controlled allocation process
- Qualitative Variables evaluated by Non-Parametric Statistics [Nominal Variable (T vs F, gender, etc) vs Ordinal Variable (Stages, 1st, etc)]
  - NB some of the parameteric statistics can also be used on qualitative variables but in general they should not be used even though they are often done
- Is the data significant by performing specific test below based on data type?
  - If it is a weird statistical test ask why

- NB Kaplan-Meier Curve
  - Compares two groups of pts (one that got the studied drug and one that didn't) and illustrates change in survival
  - Tick Marks indicate pt withdrew from study not that they died
  - The biggest issue is lead time bias (eg. with a new diagnostic test a dz could be dx much earlier which then translates into a longer measured survival after dx)



- Did the study do post hoc or retrospective subgroup analysis b/c if so then there is increased risk of finding a difference which is entirely due to chance?
- Look to see if studies statistically corrected for outlying data (eg. every data point is b/t 1-100 but one point is 10,000)

- What conclusions did the study come to?

Cohort / Case Control Studies	**Sx Reduction**	**NO Sx Reduction**
Tx	a6	b4
Placebo	c5	d5

If you are talking about good outcomes

- 50% w/ Placebo get Sx reduction but when you give Tx 60% get Sx reduction therefore the **ABI (Absolute Benefit Increase)** 60%-50% = 10% and the **RBI (Relative Benefit Increase)** = 10%/50% is 20% therefore never look at RBI b/c "looks" better and **NNT (Number Needed To Treat)** aka how many pts must get Drug Z to save one life = 1/ABI or in this case 1/.20 = 5

If you are talking about bad outcomes

- Absolute Risk Reduction and Reletive Risk Reduction (THE CALCULATION IS A LITTLE DIFFERENT)

Absolute Benefit Increase (ABI)

- Actual increase in good outcomes between treatment group patients and control group patients

(% good outcome: treatment group) – (% good outcome: control group)

Ex: 30% tx with Drug A improve; 5% tx placebo improve:
ABI= 30% - 5% = 25% OR 0.3 – 0.05 = 0.25

Relative Benefit Increase (RBI)

Increased chance of good outcome in treatment group patients *compared* to chance of good outcome in control group patients

$$\frac{\text{(\% good outcome: tx group) - (\% good outcome: cont group)}}{\text{(\% good outcome: cont group)}}$$

Ex: (.3-.05)/.05 = .25/.05 = 5 (OR 500%)

Assessing A Treatment Article

- Absolute Risk Reduction (ARR) = 0.0095 - 0.0057 = 0.0038 or 0.38%
- Number Needed to Treat = 1/ARR = 1/0.0038 = 263

Assessing A Treatment Article

Relative Risk Reduction (RRR)

$$RRR = \frac{\text{(bad outcome: placebo) - (bad outcome: treatment group)}}{\text{(bad outcome: placebo group)}}$$

$$*RRR = \frac{(0.0095 - 0.0057)}{0.0095} = 0.40 \text{ or } 40\%$$

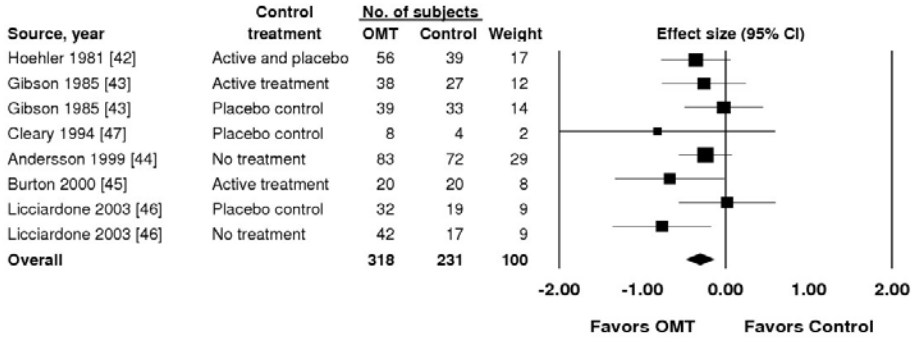
Cohort / Case Control Studies	**Get Dz**	**Don't Get Dz**
Exposure	a6	b4
No Exposure	c5	d5

- **Relative Risk: (a/a+b) / (c/c+d)**

- **Odds Ratio: (a/c) / (b/d)**

	You have the Dz	**You don't have the Dz**	• Based on the Gold Standard Test • Changes w/ Prevalence/S/S • Use these terms when considering a test in a patient (doctors should you this)
+ Diagnostic Test	a (true +)	b (false +)	**PPV (Positive Predictive Value) = a/a+b** • Given a +test how likely is it the pt actually has the dz
- Diagnostic Test	c (false -)	d (true -)	**NPV (Negative Predictive Value) = d/c+d** • Given a - test how likely is it the pt really does not have the dz
• New Test that is Being Compared to Gold Standard • No Change w/ Prevalence • Use these terms when considering a test in general populations (only epidemiologists should use this)	**Sensitivity = a/a+c** • Ability to detect dz • High for screening test	**Specificity = d/b+d** • Ability to detect health • High for confirming test	**Incidence = a+c over a period of time** **Prevalence = a+c /a+b+c+d** **Accuracy = a+d/a+b+c+d** • Tells you what proportion of the + tests had given you the correct result **Likelihood Ratio = sensitivity/1-specificity** • Tells you how much more likely a + test is found in a person w/ the dz vs w/o the dz • Eg. say 5% (pre-test probability) of the population has a disease and you see a pt and order a test that has a likelihood ratio of 3 if it is + for the disease then the pt has a 15% (post-test probability) chance having the disease

- Was the data statistically significant?
  - ***p*-value aka X^2** (very complicated formula which takes that data and sees if they are statistically significant, if *p*-value is <0.05 then there is a <5% chance that the observed outcome was actually due to chance and that the treatments are actually equally effective thus we reject the null hypothesis, remember that a study can have a *p*-value of <0.05 but still be flawed, be insignificant, etc, a p-value of 0.05 was arbitrarily chosen in that you can use any value you want but 0.05 is often chosen)
    - **Type II error = when there is actually a true difference b/t Tx and placebo but the study said there actually wasn't (Tx was the same as placebo) b/c it gave a p value of <u>>0.05</u> (this happens when a study has not entered enough pts)**
    - **Type I error = when there is actually NOT a true difference b/t Tx and placebo but the study said that there actually was (Tx was better than placebo) b/c it gave a p value of <u><0.05</u> (this happens when a study uses a biased study design b/c not randomized or blinded)**
  - **Validity/Accuracy** (How well does the study compare to the gold standard?)
  - **Reliability/Precision** (How repeatable is the study?)



  - Correlation vs Regression
    - Correlation Coefficient (aka r-value) only be done if data is normally distributed, two variables should be structurally independent, only a single pair of measurements should be made on each participant, every r-value should be accompanied by a p-value or a confidence interval
    - Regression Equation (aka y = a +bx but some equations are more complicated) that allows the target variable to be predicted from the independent variable implying a direction of influence and does not prove causality

- What are the problems w/ the study?
  - **Was biase avoided?** (there are many types of biases)
    - **Sampling** (not enough people in trial)
    - **Selection** (the way the study selected pts was not objective or random)
    - **Information** (measurements used were wrong)
    - **Confounding** (a RF is inflated b/c of some other variable)
  - Are the two groups being compared as like one another as possible except for the particular difference being examined?
  - Was the study large enough?
    - was it "powered" enough to have a high chance of detecting an effect if it exists, in order to calculate sample size the researcher needs to calculate two things: 1. What level of difference b/t the two groups would constitute a clinically significant effect? and 2. What is the mean and standard deviation of the principle outcome variable? Once you determine these two things the sample size can be easily computed using specific formulas/nomograms/tables, thus the researcher before the trial can determine how large a sample they will need in order to have a moderate/high chance of detecting a true difference b/t groups, this likelihood is the "power" which commonly is 80-90% (eg. "for a 90% chance of detecting a difference in mortality using the **** test, 100 pts were needed in each group, assuming SD of 1wk survival), under-power is common b/c it is hard to recruit pts and these studies often lead to Type II beta errors
  - Was the study long enough?
  - How complete was the f/u?
    - why did pts withdraw? Some reasons might bias the results therefore it is important to analyze the results of comparative studies on an "intent-to-treat" basis meaning that all data on participants originally allocated to the intervention arm of the study should be analyzed along with data on the pts who followed the protocol throughout, you should always read in a paper "results were analyzed on an intent-to-treat basis"
  - Drug Trials
    - Effectiveness requires a RCT, PK/PD requires experiments in healthy individuals, Long term adverse events requires long term prospective analysis
    - Tricks of the Trade: create a plausible mechanism for a drug and thus create surrogate end point, very selected population, compare drug to placebo and not to competitor drug, omit prior trials, change the axis on graphs so they look more impressive, provide quotes from experts
    - Surrogate Endpoint: an easily measured variable that is touted to predict an outcome but which is not itself a direct measure of either harm or benefit, eg. lab value, PK/in vitro measurements, macroscopic tissue/radiographic appearance, etc
    - Always ask reps about STEP (safety, tolerability, efficacy, price)